

## Predictors and consequences of fatigue in prevalent kidney transplant recipients

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## **Title**

The Predictors and Consequences of Fatigue in Prevalent Kidney Transplant Recipients

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### **Author's Contributions**

Winnie Chan, Jos A Bosch, David Jones, Nicholas Inston, Andrew McClean, Lorraine Harper and Richard Borrows participated in research design. Winnie Chan, Jos A Bosch, David Jones, Philip G McTernan, Lorraine Harper, Anna C Phillips and Richard Borrows participated in the writing of the paper. Winnie Chan, Okdeep Kaur, Sue Moore and Richard Borrows participated in the performance of the research. Winnie Chan and Richard Borrows participated in data analysis.

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### **Conflict of Interest**

The authors declare no conflicts of interest.

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## **Abbreviations**

Kidney Transplant Recipients ( <b>KTRs</b> )	Index of Co-Existent Disease ( <b>ICED</b> )
Quality of Life ( <b>QoL</b> )	Chronic Fatigue Syndrome ( <b>CFS</b> )
Multi-Dimensional Fatigue Inventory ( <b>MFI-20</b> )	Fat Tissue Index ( <b>FTI</b> )
General Fatigue ( <b>GF</b> )	Lean Tissue Index ( <b>LTI</b> )
Physical Fatigue ( <b>PF</b> )	Hospital Anxiety and Depression Scale ( <b>HADS</b> )
Reduced Activity ( <b>RA</b> )	Pittsburgh Sleep Quality Index ( <b>PSQI</b> )
Reduced Motivation ( <b>RM</b> )	Multiple Sclerosis ( <b>MS</b> )
Mental Fatigue ( <b>MF</b> )	Common-Method Variance ( <b>CMV</b> )
Medical Outcomes Study Short Form ( <b>SF-36</b> )	Trial to Reduce cardiovascular Events with Aranesp Therapy ( <b>TREAT</b> )
Kidney Transplantation ( <b>KT</b> )	

## **Abstract**

**Background:** Fatigue has been under-investigated in stable kidney transplant recipients (KTRs). The objectives of this study were to investigate the nature, severity, prevalence and clinical awareness of fatigue in medically stable KTRs, examine the impact of fatigue on quality of life (QoL), and explore the underlying causes of post-transplant fatigue.

**Methods:** This single-centre cross-sectional study enrolled 106 stable KTRs. Multi-Dimensional Fatigue Inventory (MFI-20) was used to measure 5 fatigue dimensions: General Fatigue (GF), Physical Fatigue (PF), Reduced Activity (RA), Reduced Motivation (RM), Mental Fatigue (MF). Clinical awareness of fatigue was determined by reviewing medical records. QoL was assessed by Medical Outcomes Study Short Form (SF-36) Questionnaire. Demographic, clinical, psychosocial and behavioural parameters were evaluated as fatigue predictors.

**Results:** Fatigue was found in 59% of KTRs. Only 13% had this symptom documented in medical records. Fatigue in KTRs was in the same range as chronically unwell patients, with PF, RA and RM approached levels observed in chronic fatigue syndrome. All fatigue dimensions significantly and inversely correlated with QoL ( $p < 0.001$  for all associations). Demographic predictors were male, older age and non-Caucasian ethnicity ( $p \leq 0.05$  for all associations). Clinical predictors included elevated hsCRP (inflammation), decreased eGFR (graft dysfunction), and reduced lean tissue index ( $p \leq 0.05$  for all associations). Psychosocial and behavioural predictors were inferior sleep quality, anxiety and depression ( $p < 0.01$  for all associations).

**Conclusions:** Fatigue is common and pervasive in clinically stable KTRs. It is strongly associated with reduced QoL. This study identified modifiable fatigue predictors, and sets the scene for future interventional studies.

## **Introduction**

Fatigue is an important patient-reported outcome in many medical conditions (1, 2) and involves physical (e.g. feeling exhausted and tired), cognitive (e.g. impaired concentration), emotional (e.g. lack of motivation) and functional components (3). It is often medically unexplained (4) and persistent (2), and interferes with an individual's ability to function in important roles (e.g. work, family, social life, self-care) (5). As a corollary, fatigue can have a major negative impact upon quality of life (QoL) (6).

In chronic dialysis patients, fatigue is frequently reported as a pervasive and distressing symptom (7-9). For many of these patients, kidney transplantation (KT) is the preferred modality of renal replacement therapy (10). KT increases long term survival (10), improves QoL (11), demonstrates cost benefits (12), and results in enhanced sense of well-being. Consequently, it might be assumed that fatigue no longer feature as a major problem following KT, but in fact there has been very little research to either confirm or refute this assumption. Only one study has specifically examined fatigue following transplantation (13), noting the symptom was reported in 59% of kidney transplant recipients (KTRs) and that it negatively impacted on virtually every aspect of the QoL (13). Poor sleep quality, mood disturbance and raised body mass index were identified as significant predictors for post-transplant fatigue (13). However, other potentially modifiable contributors to fatigue such as body composition, inflammation, renal function, and other biochemical markers were not examined and warrant further investigation.

Greater insight into fatigue severity, its impact on QoL, and its possible underlying causes are all pre-requisites for developing interventions to combat this symptom. In addition, it is also important to know the extent to which clinicians are aware of the problem. Therefore, the objectives of this study were to determine the nature, severity, prevalence and clinical awareness of post-transplant fatigue in a clinically-stable prevalent kidney transplant cohort. Additionally, this study aimed to examine the impact of this symptom upon QoL, and to explore the predictors of post-transplant fatigue.

## **Results**

### **Patient characteristics**

The characteristics of the studied population are shown in **Table 1**.

### **Relationship between different domains of fatigue**

The correlations between different domains of fatigue are shown in **Table 2**.

### **Nature, severity and prevalence of fatigue**

The nature and severity of fatigue are shown in **Table 3**, alongside normative data obtained from Lin's study (14). Comparison of the Multi-Dimensional Fatigue Inventory (MFI-20) subscales indicated that significant differences were found between the following dimensions: General Fatigue [GF] and Reduced Activity [RA] ( $p=0.002$ ); GF and Reduced Motivation [RM] ( $p<0.001$ ); GF and Mental Fatigue [MF] ( $p<0.001$ ); Physical Fatigue [PF] and RA ( $p=0.002$ ); PF and RM ( $p<0.001$ ); PF and MF ( $p<0.001$ ); RA and RM ( $p<0.001$ ); RA and MF ( $p<0.001$ ). The differences between the following dimensions were not statistically significant: GF and PF ( $p=0.881$ ); RM and MF ( $p=0.801$ ). In summary, physical aspects of fatigue (GF and PF) in KTRs were scored significantly higher than behavioural, emotional and cognitive aspects of fatigue (RA, RM and MF). Overall, the mean MFI-20 scores in KTRs exceeded the mean scores found in the general population and were comparable to the mean scores reported by chronically unwell patients. In fact, the mean scores for PF, RA and RM approached the mean values reported by Chronic Fatigue Syndrome (CFS) patients.

Based on the dichotomous classification of fatigue ( $\geq$  upper 95<sup>th</sup> percentile for the general population, see **Materials and Methods**), a total of 63 patients (59%) reported fatigue on at least one MFI-20 subscale. Of these 63 patients, 24% experienced GF, 38% displayed PF, 35% demonstrated RA, 29% indicated RM, and 25% revealed MF. Importantly, only 8 patients (13%) had complaints of fatigue documented in medical records.

### **Fatigue and quality of life**



As shown in **Table 4**, all dimensions of fatigue (GF, PF, RA, RM and MF) were significantly and inversely correlated with all aspects of QoL including SF-36 physical health, SF-36 mental health and SF-36 total score. To exclude the confounding effect of the SF-36 “energy and vitality” subscale, which is a general measure of fatigue within the SF-36 (15), results were reanalysed after removal of this subscale, results were comparable after this exclusion (shown in parentheses in **Table 4**).

### **Factors predicting dimensions of fatigue**

Linear regression analyses, to identify predictors of each fatigue dimension, were performed in 3 stages. First, univariate analyses tested the predictive value of each parameter individually. Second, multivariate analyses tested the independent prediction of all parameters. Third, the analysis was adjusted for anxiety, depression, and sleep quality, thereby focusing on clinical, anthropometric and laboratory parameters.

#### ***General Fatigue***

The univariate analyses are shown in **SDC, Table 5a**. In multivariate analysis, only depression ( $\beta=2.8$ ; 95% CI=1.9, 3.7;  $p<0.001$ ) and inferior sleep quality ( $\beta=1.1$ ; 95% CI=0.2, 1.9;  $p=0.01$ ) were independently associated with GF (**SDC, Figure 1** and **SDC, Figure 2**). Repeating the multivariate analysis excluding Hospital Anxiety and Depression Scale (HADS) and Pittsburgh Sleep Quality Index (PSQI) revealed that increasing time post-transplantation ( $\beta=0.6$ ; 95% CI=0.0, 1.1;  $p=0.04$ ), inflammation ( $\beta=1.8$ ; 95% CI=0.3, 3.3;

$p=0.02$ ), and renal dysfunction ( $\beta=-0.4$ ; 95% CI=-0.8, 0.0;  $p=0.04$ ) were independently associated with increasing fatigue.

### ***Physical Fatigue***

The univariate analyses are shown in **SDC, Table 5b**. In the multivariate model, depression ( $\beta=3.2$ ; 95% CI=2.3, 4.1;  $p<0.001$ ), renal dysfunction ( $\beta=-0.7$ ; 95% CI=-1.4, -0.5;  $p<0.001$ ; **SDC, Figure 3**), inflammation ( $\beta=1.4$ ; 95% CI=0.0, 2.7;  $p=0.05$ ), reduced LTI ( $\beta=-0.5$ ; 95% CI=-0.8, -0.3;  $p<0.001$ ; **SDC, Figure 4**) and male ( $\beta=2.4$ ; 95% CI=0.9, 4.0;  $p=0.003$ ) were independently associated with PF. Repeating the multivariate analysis excluding HADS and PSQI showed that renal dysfunction ( $\beta=-0.8$ ; 95% CI=-1.2, -0.4;  $p<0.001$ ), inflammation ( $\beta=2.6$ ; 95% CI=1.0, 4.1;  $p=0.002$ ), increasing time post-transplantation ( $\beta=0.7$ ; 95% CI=0.2, 1.3;  $p=0.01$ ), reduced LTI ( $\beta=-0.6$ ; 95% CI=-0.9, -0.3;  $p<0.001$ ), and male ( $\beta=3.1$ ; 95% CI=1.2, 5.0;  $p=0.001$ ) were independently associated with PF.

### ***Reduced Activity***

The univariate analyses are shown in **SDC, Table 5c**. In the multivariate model, depression ( $\beta=3.4$ ; 95% CI=1.9, 3.7;  $p<0.001$ ), inflammation ( $\beta=2.7$ ; 95% CI=1.2, 4.1;  $p<0.001$ ; **SDC, Figure 5**), and increasing age ( $\beta=0.7$ ; 95% CI=0.2, 1.1;  $p=0.003$ ) were independent predictors for RA. Following exclusion of HADS and PSQI, inflammation ( $\beta=3.8$ ; 95% CI=2.2, 5.4;  $p<0.001$ ), increasing comorbidity ( $\beta=3.4$ ; 95% CI=1.0, 5.7;  $p=0.006$ ), increasing time post-transplantation ( $\beta=0.6$ ; 95% CI=0.0, 1.2;  $p=0.04$ ), and increasing age ( $\beta=0.6$ ; 95% CI=0.2, 1.1;  $p=0.04$ ) were independently associated with RA.

### ***Reduced Motivation***

The univariate models are shown in **SDC, Table 5d**. In the multivariate analysis, depression (Odds Ratio = 1.40; CI=1.30, 1.52;  $p<0.001$ ), renal dysfunction (Odds Ratio = 0.96; CI=0.93, 1.00;  $p=0.03$ ), and reduced LTI (Odds Ratio = 0.98; CI=0.96, 1.00;  $p=0.05$ ) were associated with RM independently. Following exclusion of HADS and PSQI, increasing time post-transplantation (Odds Ratio = 1.07; CI=1.01, 1.13;  $p=0.02$ ), renal dysfunction (Odds Ratio = 0.95; CI=0.92, 0.99;  $p=0.02$ ), and inflammation (Odds Ratio = 1.22; CI=1.05, 1.43;  $p=0.01$ ) were independent predictors for RM.

### ***Mental Fatigue***

Finally, the univariate analyses predicting MF are shown in **SDC, Table 5e**. In the multivariate model, only anxiety was independently associated with fatigue (Odds Ratio = 1.36; CI=1.24, 1.49;  $p<0.001$ ; **SDC, Figure 6**). A borderline effect of ethnicity was found (Odds Ratio = 1.42; CI=1.01, 1.99;  $p=0.05$ ). When the multivariate analysis was repeated excluding the HADS and PSQI results, no predictor variables retained statistical significance.

## **Discussion**

This study aimed to investigate the nature, severity, prevalence and clinical awareness of post-transplant fatigue, determine the association between fatigue and QoL, and identify main predictors of post-transplant fatigue. The results revealed that in clinically stable KTRs without evidence of intercurrent disease, fatigue is common, severe, and clinically under-

appreciated. It has a close association with inferior QoL. These results confirm and

significantly extend the findings of the single previous study on post-transplant fatigue (13), and advances understanding of the possible determinants of fatigue by showing associations with anthropometric and clinical variables not previously evaluated. Depression, anxiety, inferior sleep quality, inflammation, reduced muscle mass, and renal dysfunction were identified as risk factors, forming potential targets for future interventional studies.

The significant correlations between different domains of fatigue suggest that treatment of behavioural, emotional and cognitive aspects of fatigue may improve physical aspects of fatigue, or vice versa. However, a recent study provides experimental evidence that mental fatigue limits exercise tolerance in humans via higher perception of effort rather than cardiorespiratory and musculoenergetic mechanisms (16), implying that the overall focus of fatigue management should be on the behavioural, emotional and cognitive aspects.

Compared to normative data from healthy population (14, 17), KTRs suffer from higher levels of fatigue on all dimensions. In comparison to normative data from Lin (14), fatigue levels in KTRs were similar to “chronically unwell” patients, defined as having chronic ( $\geq 6$  months) unwellness with or without fatigue, but not meeting criteria for CFS (14). Indeed, severity in certain domains, such as PF, RA and RM, approached that of CFS (14), further highlighting the burden of fatigue in KTRs. Of note, the level of MF was higher in KTRs compared to cancer patients with mild anaemia undergoing chemotherapy (17), and chronic heart failure patients with and without anaemia (18). Also, KTRs suffer from higher levels of PF, RA and RM compared to cancer patients without anaemia (17). Physical aspects of

fatigue outweighed behavioural, emotional and cognitive aspects, resembling findings in liver transplant recipients (19).

Using a dichotomous fatigue definition, 24-38% of participants reported fatigue in at least one of the five dimensions, and 59% in any dimension. This prevalence is comparable to that found by Rodrigue (13) using the one-dimensional “Fatigue Symptom Inventory”. Despite the high prevalence, only 13% of patients had fatigue documented in medical records prior to participation in this study, suggesting that this symptom is either under-reported or under-acknowledged. Furthermore, the close correlation between all fatigue domains and QoL resonates with the clinical and social relevance of this symptom.

The assessment of multiple domains of fatigue, and the measurement from the clinically validated HADS extends the findings of Rodrigue (13) where fatigue severity significantly correlated with a composite mood score incorporating depression, vigour, anger, confusion, anxiety and fatigue itself. The current study highlights the specific, independent importance of depression as a risk factor for all dimensions of fatigue except for MF. This exception is surprising as previous study on multiple sclerosis (MS) related fatigue found that depression was related to MF (20, 21). However, depression and MF can occur independently or simultaneously (22), this phenomenon has been demonstrated in stroke patients (22). Many symptoms for depression and MF overlap, but the core symptoms are different. The lack of association in this study may be explained by the distinction between the core symptoms. Depression is an illness or mood disorder with a variety of symptoms, the most defining being an inexplicable, enduring feeling of sadness, and loss of positive affect (23). The collective symptoms may not manifest as MF, which is a psychobiological state caused by

prolonged periods of demanding cognitive activity such as concentration, attention and

increased mental load (16). In MF, mental effort can only be sustained for a short time-frame, and recovery period is disproportionally long (22). Accompanying symptoms include irritability, sensitivity to stress, concentration difficulties, and emotional instability (22).

Anxiety was a significant predictor for MF, similar to other chronic conditions such as MS (21). KTRs are subjected to several mental challenges, including fears about transplant rejection and the necessity to adhere to a complex regimen of immunosuppression therapy that may generate distressing side effects (24). To an extent, the unpredictable clinical course post-transplantation is reminiscent of the relapsing and remitting nature of MS. While acknowledging the limitations of cross-sectional data to make causal inferences, the present results are in line with evidence showing that psychological interventions addressing disease-related anxiety and depression *per se* may yield added benefit in modifying fatigue.

While inferior sleep quality may intuitively be expected to have a pervasive and broad effect on multiple aspects of fatigue (13), a significant association was only observed for the GF dimension. This finding suggests that mere sleep difficulties do not explain a large spectrum of the fatigue complaints in KTRs, and interventions aiming to improve sleep quality may have limited effect on fatigue.

An important caveat with the interpretation of the associations between self-reported data, such as depression, sleep difficulties and symptoms of fatigue is that common-method variance (CMV) may partly drive the observed associations, and may account for 25% of shared variance (25). In CMV, patients high in negative affect (i.e. negative mood) perceive, remember and report more physical and psychological symptoms, and report those symptoms

to be more severe than patients with a less negative mood (26). Additionally, individual items on questionnaires measuring fatigue, depression or sleep problems tend to show conceptual overlap, which further enhances co-variation. While these would not render self-reports unimportant, and neither would refute that sleep and depression may have strong bidirectional links with fatigue, potential interpretational difficulties may result. Therefore, this study's detailed anthropometric and biochemical data represents an important extension of the previous study in the field (13). When multivariate regression analysis excluded adjustment for mood and sleep, reduced LTI, renal impairment and inflammation were identified as potentially reversible predictors.

The association between inflammation and fatigue is particularly notable as the studied cohort consisted of clinically stable KTRs, without overt evidence of ongoing acute or chronic inflammatory conditions. Evidence from studies of healthy volunteers, elderly populations and other disease groups have shown that inflammatory cytokines possess potent neurological effects and are mediators of fatigue (13, 27-30). Modifying inflammation may therefore represent an attractive target in future studies.

The independent association between physical fatigue and reduced LTI is intuitively plausible, but not previously reported in KTRs. It replicates results from cancer-related fatigue (31), and fatigue associated with end-stage renal disease on haemodialysis (32, 33). Reduced muscle mass coupled with increased fat mass ("sarcopenic obesity") is a common characteristic of body composition following KT (34). Despite significant univariate associations between FTI and different dimensions of fatigue (GF, PF, RA and RM), this relationship did not hold when adjusted for inflammation, suggesting inflammation as the

driver for fatigue, rather than adiposity per se. This study advances understanding from

Rodrigue (13) where raised BMI (a proxy for fat mass) was identified as a predictor of

fatigue, but detailed anthropometric and inflammatory evaluation was not undertaken.

However, it is possible that the systemic low-grade inflammation present in obesity triggers

adipocyte release of pro-inflammatory cytokines (35), this in turn accelerates muscle

catabolism (36), leading to muscle wasting (36). The current study suggests that lifestyle

interventions with a strong focus on increased physical activity and dietary modification

aiming to reverse this phenotype should be valuable for patients displaying symptoms of

fatigue. Apart from promoting favourable changes in body composition, lifestyle

modification is particularly important in light of the inverse associations between all domains

of fatigue and SF-36 physical health subscale, which is a representation of self-perceived

physical functioning. Recent studies reported that self-perceived physical functioning is

significantly and positively correlated with physical activity level (37, 38). Although

physical activity level was not measured in the current study, this finding suggests that

striving to be physically active enhances functional capacity and improves self-perception of

physical functioning, leading to improved fatigue and quality of life.

Although fatigue is a common and important symptom for patients on dialysis (7, 8), the

present results show, for the first time, a relationship between allograft dysfunction and

physical fatigue in KTRs. Clinical strategies exist to improve allograft function (39) and

fatigue may represent an important patient-reported outcome in future interventional studies.

Other non-modifiable, but important, risk factors for varying domains of fatigue included

male, older age, ethnicity, comorbidity, and increasing time post-transplantation.



The lack of association between haemoglobin level and fatigue is unsurprising as the results from the TREAT study (Trial to Reduce cardiovascular Events with Aranesp Therapy) (40) only showed a small improvement in fatigue with haemoglobin normalisation, using recombinant erythropoietin in non-transplant, diabetic, chronic kidney disease.

The use of immunosuppressive medication was not associated with fatigue in KTRs. Of relevance, no link between immunosuppression and fatigue was seen in previous studies of liver transplant recipients (19) and KTRs (13).

This study has limitations that should be acknowledged. It is a single-centre study with a small sample size. The progression and regression of fatigue over time could not be evaluated due to the study design of cross-sectional nature. The results may not be representative of “sicker” patients within the transplanted population. It is recognised that hyperparathyroidism occurs in a substantial proportion of KTRs (17%) (41), with fatigue as a possible manifestation. Unfortunately, serum parathyroid hormone concentrations were not routinely measured in this study.

Whilst kidney transplantation is associated with a variety of benefits compared with dialysis, this study shows that fatigue remains a common and relevant problem in otherwise stable KTRs. As the medical complexity of KTRs increases, it is important not to lose sight of important patient-reported outcomes such as fatigue. This study demonstrates potential

targets for intervention, and future research should focus on evaluating the effectiveness and impact of such interventions upon fatigue and QoL.

## **Materials and Methods**

### **Participants and study design**

Stable KTRs beyond 1 year post-transplantation, with stable graft function (<10% increase in serum creatinine over preceding 6 months) were recruited to this cross-sectional study from the renal transplant outpatient clinic at Queen Elizabeth Hospital Birmingham UK, between April 2010 and April 2012. Exclusion criteria included episodes of acute rejection within the last 6 months, evidence of sepsis in the last 6 weeks, known active malignancy or chronic infection, preceding diagnosis of psychiatric disorder or chronic fatigue syndrome, and history of thyroid disease or adrenal insufficiency.

Of 114 eligible patients approached, n=6 refused to participate and n=2 did not attend the research visit. Reasons for declining entry were work commitment (n=4) and participation in other studies (n=2). The study was approved by the local research ethics committee, and was conducted in accordance with the principles of the Declaration of Helsinki.

Patients attended the research visit following a 10-hour overnight fast. The order of tests was standardised. A fasting blood sampling was taken, followed by a light breakfast before bio-

impedance body composition assessment, and self-completion of questionnaires under

supervision of the researcher (see below).

## **Fatigue measurement**

Severity and nature of fatigue were determined using the MFI-20, which is a 20-item self-report questionnaire that measures fatigue in 5 primary dimensions: General Fatigue (GF); Physical Fatigue (PF); Reduced Activity (RA); Reduced Motivation (RM); Mental Fatigue (MF). The physical aspects of fatigue are captured by GF and PF; and the behavioural, emotional and cognitive aspects of fatigue are represented by RA, RM, and MF (42) (see **SDC, Materials and Methods** for scoring and description of MFI-20).

A consensus definition for clinically meaningful fatigue is lacking. In this study, KTRs were considered fatigued if scores for any dimension was  $\geq$  upper 95<sup>th</sup> percentile for the general population as reported by Lin (14) (GF  $\geq$  15; PF  $\geq$  14; RA  $\geq$  12; RM  $\geq$  12; MF  $\geq$  13). The present data were also compared with two other clinical groups, similarly derived from Lin (14), namely patients with CFS and patients with other chronic (> 6 months) diseases.

Reporting of fatigue by clinicians was assessed by retrieving medical records for the 4 clinic visits prior to participation in this study (see **SDC, Materials and Methods** for explanation of medical record retrieval).

## **Quality of life assessment**

QoL was assessed using the Medical Outcomes Study Short Form 36 (SF-36) questionnaire, which generates the total score for QoL, as well as physical health and mental health sub-scores (see **SDC, Materials and Methods** for scoring and description of SF-36).

## **Factors associated with fatigue**

### ***Demographics and clinical parameters***

Age, gender, marital status, ethnicity, and time post-transplantation were collected from patients' medical records. Smoking status (never smoked, current smoker, ex-smoker) and alcohol intake (units per week) were collected by questionnaire. Co-morbidity was assessed by Index of Co-Existing Disease (ICED), using the algorithm described by the Hemodialysis (HEMO) Study (43), with data extracted from patients' medical records. Presence of diabetes, either pre-transplantation (pre-DM) or new onset diabetes after transplantation (NODAT), prior acute rejection episodes, and immunosuppressive medication usage were retrieved from patients' medical records.

### ***Laboratory parameters***

Fasting blood sample was taken for analysis of high sensitive C-reactive protein (hsCRP), haemoglobin (Hb) and estimated glomerular filtration rate (eGFR) derived using the 4-variable modification of diet in renal disease equation (44).

### ***Body composition***

Body composition was assessed by multi-frequency bio-impedance measurement, using the body composition monitor to provide values for Lean Tissue Index (LTI) and Fat Tissue Index (FTI) (see **SDC, Materials and Methods** for explanation of bio-impedance measurement).

### ***Self-reported outcome measures***

Anxiety and Depression were assessed using the Hospital Anxiety and Depression Scale (HADS) (45). Sleep quality was assessed by the Pittsburgh Sleep Quality Index (PSQI) (46). See **SDC, Materials and Methods** for scoring and description of HADS and PSQI.

### **Statistical analysis**

Statistical analysis was performed using STATA. Results are presented as mean  $\pm$  standard deviation or median (interquartile range). Independent sample *t*-tests were used to compare continuous variables, and Pearson correlation coefficients to assess relationship.

Linear regression analysis was used to determine predictor variables associated with different domains of fatigue. The analyses were performed in two stages. Initially, the effect of each variable was examined in a series of univariate analyses. Subsequently, the joint effect of variables was examined in a multivariate analysis, using a backwards selection procedure to derive the final model. A type 1 error rate  $\leq 5\%$  ( $p \leq 0.05$ ) was considered significant. Results

for GF, PF and RA revealed normal distributions and were analysed on the original scale of measurement. Results for RM and MF demonstrated positively skewed distributions and underwent logarithmic transformation prior to analysis. In the multivariate regression analyses, only the explanatory variables with univariate *p*-values of <0.20 were included. The figures reported in **SDC, Tables 5a, 5b, 5c, 5d and 5e**, were regression coefficients or odds ratios, and their corresponding confidence intervals. The regression coefficients and odds ratios describe the change in fatigue for the described increase (or category) of the predictor variable.

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**Table 1: Population Characteristics**

	Characteristics
<b>Sample size</b>	n = 106
<b>†Mean age</b>	51 ± 14 years
<b>Gender</b>	56% Male; 44% Female
<b>Marital status</b>	Single 21%; Married 71%; Divorced/Widowed 8%
<b>Immunosuppressive medication usage</b>	
Calcineurin inhibitor	89% (55% Tacrolimus, 34% Cyclosporin)
Adjunctive antiproliferatives	87% (58% Mycophenolate Mofetil, 29% Azathioprine)
Prednisolone	74%
<b>Dosage of immunosuppressive medications</b>	
‡Median dose of Tacrolimus	4.0 (2.5-6.0) mg/day
‡Median dose of Cyclosporin	150 (150-200) mg/day
†Mean dose of Mycophenolate Mofetil	987 ± 392 mg/day
†Mean dose of Azathioprine	77 ± 36 mg/day
†Mean dose of Prednisolone	5.2 ± 1.0 mg/day
<b>*Ethnicity</b>	
Caucasian	76%
Afro-Caribbean	7%
Asian	15%
Other	2%
<b>‡Median time post transplantation</b>	6.5 (3.0-14.0) years
<b>‡Median alcohol intake per week</b>	0.0 (0.0-3.0) units
<b>Smoking status</b>	
Never smoked	63%
Current smoker	7%
Ex-smoker	30%
<b>†**Mean ICED score (co-morbidity)</b>	2.1 ± 0.4
Score = 1	2%
Score = 2	85%
Score = 3	13%
<b>†Mean Hb</b>	12.6 ± 1.6 g/dl
<b>‡Median hsCRP</b>	2.5 (1.0-4.9) mg/l
<b>†Mean eGFR</b>	43.9 ± 18.5 ml/min
<b>Body composition</b>	
†Mean lean tissue index (LTI)	13.9 ± 3.0 kg/m <sup>2</sup>
†Mean fat tissue index (FTI)	14.2 ± 6.2 kg/m <sup>2</sup>
<b>HADS</b>	
‡Median anxiety score	6.0 (2.5-9.5)
‡Median depression score	3.0 (1.0-7.0)
<b>PSQI</b>	
†Mean global score	7.2 ± 4.1

†Normally distributed data, results expressed as mean ± SD. ‡Non-normally distributed data, results expressed as median (Interquartile Range). \*For the purpose of the statistical analysis, the ethnicity of 2% of patients classified as "Other" was grouped as "Caucasian". \*\*For the purpose of the statistical analysis, the Index of Co-Existent Disease (ICED) scores were arranged into 2 categories (≤2 versus >2, 87% and 13% of patients respectively).

**Table 2: Correlation between different domains of fatigue**

Pearson correlation ( $r$ );  $p$ -value for each correlation

	<b>General Fatigue (GF)</b>	<b>Physical Fatigue (PF)</b>	<b>Reduced Activity (RA)</b>	<b>Reduced Motivation (RM)</b>	<b>Mental Fatigue (MF)</b>
<b>General Fatigue (GF)</b>		$r=0.74$ ; $p<0.001$	$r=0.68$ ; $p<0.001$	$r=0.65$ ; $p<0.001$	$r=0.46$ ; $p<0.001$
<b>Physical Fatigue (PF)</b>	$r=0.74$ ; $p<0.001$		$r=0.76$ ; $p<0.001$	$r=0.69$ ; $p<0.001$	$r=0.34$ ; $p<0.001$
<b>Reduced Activity (RA)</b>	$r=0.68$ ; $p<0.001$	$r=0.76$ ; $p<0.001$		$r=0.62$ ; $p<0.001$	$r=0.32$ ; $p=0.001$
<b>Reduced Motivation (RM)</b>	$r=0.65$ ; $p<0.001$	$r=0.69$ ; $p<0.001$	$r=0.62$ ; $p<0.001$		$r=0.46$ ; $p<0.001$
<b>Mental Fatigue (MF)</b>	$r=0.46$ ; $p<0.001$	$r=0.34$ ; $p<0.001$	$r=0.32$ ; $p=0.001$	$r=0.46$ ; $p<0.001$	

**Table 3: Nature and Severity of Fatigue**

Mean Fatigue Score  $\pm$  SD by Dimensions

	<b>Transplant Patients</b>	<b>Healthy Population<sup>†</sup></b>	<b>Chronically Unwell Patients<sup>†</sup></b>	<b>Chronic Fatigue Syndrome-like Patients<sup>†</sup></b>
<b>General Fatigue (GF)</b>	11.78 $\pm$ 4.05	8.42 $\pm$ 3.59	12.84 $\pm$ 3.84	16.38 $\pm$ 2.73
<b>Physical Fatigue (PF)</b>	11.73 $\pm$ 4.74	7.77 $\pm$ 3.36	10.39 $\pm$ 3.76	13.63 $\pm$ 3.79
<b>Reduced Activity (RA)</b>	10.69 $\pm$ 4.70	6.76 $\pm$ 2.67	9.06 $\pm$ 3.75	11.32 $\pm$ 4.37
<b>Reduced Motivation (RM)</b>	9.36 $\pm$ 3.61	6.82 $\pm$ 2.91	9.29 $\pm$ 3.35	11.95 $\pm$ 3.53
<b>Mental Fatigue (MF)</b>	9.67 $\pm$ 4.54	7.23 $\pm$ 3.07	10.98 $\pm$ 4.00	13.77 $\pm$ 3.77

<sup>†</sup>Original unpublished normative data provided by Lin et al (14).

**Table 4: Association between Fatigue and Quality of Life**

	<b>SF-36 Physical Health</b>	<b>SF-36 Mental Health</b>	<b>SF-36 Total Score</b>
<b>General Fatigue (GF)</b>	$\dagger r=-0.68; p<0.001$ $*(r=-0.62; p<0.001)$	$\dagger r=-0.70; p<0.001$ $*(r=-0.63; p<0.001)$	$\dagger r=-0.68; p<0.001$ $*(r=-0.64; p<0.001)$
<b>Physical Fatigue (PF)</b>	$\dagger r=-0.78; p<0.001$ $*(r=-0.74; p<0.001)$	$\dagger r=-0.71; p<0.001$ $*(r=-0.65; p<0.001)$	$\dagger r=-0.74; p<0.001$ $*(r=-0.72; p<0.001)$
<b>Reduced Activity (RA)</b>	$\dagger r=-0.72; p<0.001$ $*(r=-0.69; p<0.001)$	$\dagger r=-0.67; p<0.001$ $*(r=-0.62; p<0.001)$	$\dagger r=-0.71; p<0.001$ $*(r=-0.68; p<0.001)$
<b>Reduced Motivation (RM)</b>	$\dagger r=-0.66; p<0.001$ $*(r=-0.64; p<0.001)$	$\dagger r=-0.69; p<0.001$ $*(r=-0.66; p<0.001)$	$\dagger r=-0.69; p<0.001$ $*(r=-0.68; p<0.001)$
<b>Mental Fatigue (MF)</b>	$\dagger r=-0.33; p<0.001$ $*(r=-0.29; p<0.01)$	$\dagger r=-0.49; p<0.001$ $*(r=-0.48; p<0.001)$	$\dagger r=-0.42; p<0.001$ $*(r=-0.41; p<0.001)$

$\dagger$ Correlation and  $p$ -value derived from comparisons between all domains of fatigue and all SF-36 subscales in the analysis.

\*Correlation and  $p$ -value in parentheses derived from comparisons between all domains of fatigue and SF-36 excluding "energy and vitality" subscale in the analysis.